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Blood Pressure and Heat Shock Protein 70 Levels Related to Acute Ischemic Stroke Severity

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ABSTRACT

Introduction: Hypertension is a risk factor of ischemic stroke, the prevalence of ischemic stroke in Indonesia is 34.1%. Heat Shock Protein (HSP) 70 increases in hypertension and acute phase of ischemic stroke. To determine differences of blood pressure (BP) and HSP 70 levels, related to the acute ischemic stroke severity.

Methods: This was a cross-sectional study that was carried out in the Neurological Ward of Dr.M.Djamil Hospital and National Stroke Hospital, from May to September 2019. Inclusion criteria were obtained consecutively. BP was measured with a sphygmomanometer, stroke severity was measured by NIHSS, and HSP 70 levels was analyzed by the ELISA. Computerized statistical analyzes were performed using SPSS software version 23.0 for windows. The result was statistically significant if the p-value < 0.05.

Results: There were 40 samples consisted of 26 (65%) male, mean age 59.78 years. The systolic BP ranging from 130 to 190 mmHg (median 160), the diastolic BP ranging from 70 to 100 mmHg (median 90), the HSP 70 levels ranging from 2.50 to 19.56 ng/mL (median 2.72). There were 18 patients with mild stroke and 22 patients with moderate stroke. There was no significant difference between systolic blood pressure (SBP), diastolic blood pressure (DBP), and severity of stroke ($p=0,369$; $p=0,221$, respectively). There was no significant difference between HSP 70 levels and the severity of stroke ($p=0,312$). There was no relation between the degree of BP and HSP 70 levels.

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Conclusion: There were no significant differences of SBP, DBP, and HSP 70 with the acute ischemic stroke severity.

Keywords: Blood pressure; heat-shock protein 70; hypertension; sphygmomanometers; stroke

Introduction

Hypertension is the most important problem of global diseases that cause death and it is a major risk factor for ischemic stroke.¹ In Indonesia, the prevalence of hypertension in 2018 reaches 10.9:1000.² Increased blood pressure often occurs in acute stroke and generally decreases spontaneously within a few days. The mechanism of a briefly elevated blood pressure is often referred to as a stroke-specific response to maintain the perfusion pressure in the distal portion of the occluded cerebral arteries.³ In a recent study using data collected from nationwide emergency departments, there were 69% of patients had systolic blood pressure >139 mm Hg, while other studies have found BP of >150/90 mm Hg in up to 84% of patients.⁴

Several biomarkers increase in acute ischemic stroke, one of which is HSP 70.⁵ Heat shock protein (HSP) 70 is a protein that appears as cell response to acute stress, such as oxidative stress, nutritional deficiencies, ultraviolet radiation, chemicals, viruses, accumulation of oxidized LDL, increased blood pressure and ischemic reperfusion injury.^{6,7,8} The experimental studies in hypertensive mice was found elevated HSP 70 in the adventitial area of the arteries and kidney within 2 weeks.⁹ Que et al reported that HSP has a protective effect and the levels of HSP increased on the acute phase of the ischemic stroke patient.¹⁰ The immediate effect of HSP 70 on hypertension is as a protector, suppresses activation of nuclear factor kappaB (NFkB), and improves blood pressure response to angiotensin II. However, chronic overexpression of HSP 70 will be more pro-hypertensive because of its ability to trigger an autoimmune response.¹⁰

This study aims to determine whether there are differences between initial blood pressure (systolic blood pressure and diastolic blood pressure) and HSP 70 level that related to the severity of acute ischemic stroke.

Methods

This is a cross-sectional study. The sample size was obtained from the comparative analytic study formula, the results were 40 subjects. The study subject was recruited from the inpatient of Neurology Ward of Dr. M. Djamil Hospital, Padang and National Stroke Hospital, Bukittinggi. The study was held from May to September 2019.

The study subject was all patients with acute ischemic stroke who fulfill the inclusion and exclusion criteria. The inclusion criteria in this study were first-time ischemic stroke patients who were diagnosed based on history taking, neurological examination, and head CT scan, with less than 48 hours of onset, and they agree to participate in this study by signing informed consent.

Patients who suffered from bacterial infections, sepsis, history of heart disease, history of tumors, kidney disorders, and previous stroke history were excluded from this study. The sampling technique was done by using the consecutive method. All subjects who meet the inclusion and exclusion criteria were selected based on the determined sample. This research has been approved by the Medical Research Ethics Committee Team at Andalas University, Padang.

Data were obtained from blood pressure measurements when patients were hospitalized using a mercury sphygmomanometer. Serum HSP 70 levels were determined using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (@Human HSP-70 ELISA kit). The assay was performed in the Biomedic Laboratory of Andalas University. The severity of acute ischemic stroke was assessed using the National Institutes of Health Stroke Scale (NIHSS). The point of 1-5 had a mild stroke, 6-15 had a moderate stroke, and 16-24 had a severe stroke. Statistical analyzes were performed computerized using SPSS software version 23.0 for windows. Data distributed normally is presented as the mean and standard deviation (SD), whereas data distributed not normally are presented as the median and interquartile range. A comparison between variables was analyzed using the unpaired t-test for normal distribution data and Mann-Whitney U test for not normal distribution data. The fisher-exact test was used to analyze categorical data. A statistically significant relation was considered if the p-value < 0.05.

Results

There were 40 subjects (65% were men, 35% women, and mean age 59.78 years). The systolic blood pressure ranging from 130 to 190 mmHg (median 160 mmHg), and the diastolic blood pressure ranging from 70 to 100 mmHg (median 90 mmHg), while HSP 70 levels ranging from 2.50 to 19.56 ng/mL (median 2.72 ng/mL). There were 18 (45%) patients with mild strokes and 22 (55%) patients with moderate strokes, but no patients with severe stroke in table 1. Age variable has normal distribution based on normality test ($p > 0.05$), meanwhile, SBP, DBP, and HSP levels have not normal distribution. Mann-Whitney U test was used to determine the difference between variables related to stroke severity.

There were no significant differences in the initial blood pressure (systolic and diastolic) and HSP 70 levels in any of the subgroup severity of stroke ($p=0,369$; $p=0,221$; $p=0,312$; respectively). However, there was a tendency for an increase in systolic blood pressure and HSP 70 levels in the moderate stroke group compared to the mild stroke group (Table 2).

Table 1. Basic characteristics of the sample

Characteristics	Patient n=40
Age (year)	59,78 (\pm 10,42)
Sex	
Women, n(%)	14 (35)
Men, n(%)	26 (65)
Systolic Blood Pressure (mmHg)	160 (130-190)
Diastolic Blood Pressure (mmHg)	90 (70-100)
HSP 70 Level (ng/mL)	2,72 (2,50-19,56)
Mild Strokes, n (%)	18 (45)
Moderate Strokes, n (%)	22 (55)
Severe Strokes, n (%)	0 (0)

Values are expressed as frequency (%), mean \pm Standard Deviation, median(min-max)

Table 2. Differences of variables related to stroke severity

Variable	Mild Stroke, n=18	Moderate Stroke, n=22	P
Age (year)	61(\pm 8.50)	58.96 (\pm 11.63)	0.551 [#]
Sex			0,079 [∞]
Women	14 (35)	12 (30)	
Men	4 (10)	10 (25)	
SBP (mmHg)	160 (150-190)	165 (130-190)	0,369*
DBP (mmHg)	90 (90-100)	90 (70-100)	0,221*
HSP 70 (ng/mL)	2,72 (2,5-5,55)	2,79 (2,5-19,56)	0,312*

Note: [#]Unpaired t-test [∞]Fisher exact test *Mann-Whitney U test

The age variable was expressed as mean \pm Standard Deviation, sex variable was expressed as frequency (%), SBP, DBP, and HSP variables were expressed as median (minimum-maximum)

Abbreviations: SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; HSP, Heat Stroke Protein.

We also analyzed the relation between blood pressure and HSP 70 levels (Table 3). We classified systolic blood pressure based on median values into two categories which are SBP >160 mmHg and SBP \leq 160 mmHg. We classified diastolic blood pressure based on median values into two categories which are DBP > 90 mmHg and DBP \leq 90 mmHg. HSP 70 was classified into two categories which are HSP 70 > 2,72 ng/mL and HSP 70 \leq 2,72 ng/mL. The results showed no relationship between increased blood pressure (SBP and DBP) with HSP 70 levels ($p > 0.05$).

Table 3. The relation between blood pressure and HSP 70 levels

Variable	HSP 70		OR (95% CI)	P
	> 2,72 ng/mL	\leq 2,72 ng/mL		
SBP				
SBP > 160 mmHg	10 (25)	7 (17,5)	2,22 (0,62-7,98)	0,218*
SBP \leq 160 mmHg	9 (22,5)	14 (35)		
DBP				
DBP > 90 mmHg	5 (12,5)	5 (12,5)	1,14 (0,27-4,78)	1,000*
DBP \leq 90 mmHg	14 (35)	16 (40)		

*Fisher Exact Test, SBP and DBP variables were reported as frequency (%)

Discussion

This study was conducted on 40 patients who suffered an acute ischemic stroke (18 patients with mild stroke and 22 patients with moderate stroke). There was no significant difference in the initial blood pressure (systolic and diastolic) of mild stroke group as compared to that of a moderate stroke group. However, there was a tendency for an increase in systolic blood pressure in the moderate stroke group (165 mmHg) as compared to the mild stroke group (160 mmHg). Liu et al found that there was a significant difference between systolic blood pressure and the NIHSS value of acute stroke patients, where patients with higher systolic blood pressure had higher NIHSS values, but different results found in diastolic blood pressure.^{5,11} Kvistad et al reported that elevated admission blood pressure was associated with mild stroke and severe stroke.¹²

We also found no significant difference in HSP 70 levels in the mild stroke group as compared to that of a moderate stroke group. However, there was a tendency for an increase in HSP 70 levels in the moderate stroke group as compared to the mild stroke group. HSP 70 has a role as a neuroprotector as seen in endothelial cells and glial cells such as astrocytes and microglia. This has been proven by genetic mutation models.^{13,14} HSP 70 presents in the brain under normal physiological conditions, but after 10 minutes of ischemic events, the value will increase for the next 24 hours. It can increase last up to day 7.⁶ Research by Que et al, reported a decrease in HSP 70 levels comparable to improvement in functional status (NIHSS) of ischemic stroke patients.¹⁰

A study in animals reported that there was a relationship between increased blood pressure and HSP 70 expression, which is a physiological response to acute hypertension and HSP 70 had a role in protecting blood vessel vascularity from damage during hemodynamic stress. Based on these reports, we also tried to find a relation between increasing blood pressure with HSP 70 levels in this hemodynamic stress condition (acute ischemic stroke). We found no significant relationship between the degree of blood pressure (systolic and diastolic) and HSP 70 levels, which contradicted with result in the experimental animal study. This could be due to differences in sample conditions. There were structural lesions that underlie the occurrence of increased blood pressure. However, our results are in accordance with a recent cross-sectional study, in which there was no relation of HSP 70 levels with risk factors for cardiovascular disease (including hypertension).¹⁵

Although no significant relationship found between blood pressure and HSP 70 levels, patient with SBP > 160 mmHg have the possibility of HSP 70 levels that are 2.22 times higher than patient with SBP ≤160 mmHg and patients with DBP > 90 mmHg have the possibility of HSP levels 70 which is 1.14 times higher than patient with DBP <90 mmHg.

There are some limitations in this study which might be a reference for further research. Analysis of the control sample with a larger sample size should be studied in the future to achieve a better comprehension of the topic.

In this study, the evaluation of morbidity and mortality due to initial blood pressure increasing in acute ischemic stroke was not assessed because our study was cross-sectional. We can not find the variability of HSP 70 levels related to functional outcomes in ischemic stroke patients.

Conclusion

There is no significant difference between initial blood pressure (systolic and diastolic), and HSP 70 level related to the severity of acute ischemic stroke. It is recommended to conduct further research on a larger scale with other related variables.

Conflicts of Interest

There is no conflict of interest.

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